

## **EXHIBIT B**

## Clinical trial (Phase II)

This clinical study comprised three groups of patients that received:

Group I: Suppositories of 2 g containing the Placebo, composed by the excipients without sodium salicylate (19 patients).

Group II: Suppositories of 2 g containing Placebo plus sodium salicylate (20 patients).

Group III: Suppositories of 2 g containing excipients, sodium salicylate and 200 000 IU of Recombinant Streptokinase (21 patients).

**Table # 1** shows the distribution of patients according to the main variable of evaluation, the Healing, defined as a reduction of more than 90% of the size of the initial lesion and without the presence of pain and edema. As it can be observed, a significant dependence is detected between the success and the treatment received, in particular because of the superiority of group III that received Recombinant Streptokinase (200 000 IU) with respect to placebo (group I), with a punctual difference estimated in 36.8% (IC 95%: 12 - 62).

**Table # 1. Assortment of patients according to treatment group and the Healing of the acute hemorrhoidal disease at 5th day (Main Variable).**

TREATMENT		Group I (Placebo)	Group II (Placebo + Salicylate)	Group III (SK-200 000 UI)	T ( $\chi^2$ )
N		19	20	21	
Healing after 5 days	Yes	3 (15.8%)	6 (30.0%)	11 (52.4%)	0.023
	No	16 (84.2%)	14 (70.0%)	10 (47.6%)	

It was considered **Healing** all patients with Total Response in the evaluation at 5 days, given by the complete disappearance of pain and edema, and the reduction of more than 90% of the initial size of the lesion with absence of relapse nor need of thrombectomy.

With respect to the time of Healing, a speed of Healing significantly higher in group III (SK – 200 000 IU) is detected with respect to the rest of the groups (I: placebo and II: placebo + Salicylate), with a median estimated in 5 days, while in the rest of the groups the median is found approximately in 10 – 11 days.

**Table # 2** shows the results with respect to the secondary variable at 5 days (Total Response: decrease of more of a 70% size of the initial lesion and elimination of the pain and edema).

At 5 days, in group III (SK 200 000 UI) there was Total Response in 66.7% of the patients treated, while in groups I and II the proportion of patients with Total Response reached 36.8% and 35.0%, respectively. In this evaluation (5<sup>th</sup> day), the independence probability diminishes to 0.361, observing evidences on favor of the

difference among the groups (FB=1.769) specifically group III (SK – 200 000 IU) with respect to Placebo (median difference estimated in 29.7%) and with respect to group II that received placebo + Salicylate (median difference estimated in 32.4%).

**Table # 2. Assortment of patients according to the evaluation of the response at 5 days, by treatment group.**

TREATMENT		Group I	Group II	Group III	T ( $\chi^2$ ) melting PR + No remission
N		19	20	21	
5 days	<i>TR</i>	7 (36.8%)	7 (35.0%)	14 (66.7%)	0.106
	<i>PR</i>	6 (31.6%)	9 (45.0%)	3 (14.3%)	
	<i>No remission</i>	6 (31.6%)	4 (20.0%)	4 (19.0%)	

The answer at the 5<sup>th</sup> day was evaluated according to the following criteria:

**Total Response (TR):** Complete disappearance of the pain and the edema, and reduction of more than 70% of the initial size of the lesion.

**Partial Response (PR):** Presence of pain but with reduction of two levels in the intensity and/or disappearance of the edema (or more than 50% reduction of the size of the lesion).

**Non remission:** No reduction of the pain in two levels of intensity and presence of edema and no reduction of the size of the lesion or reduction of less than 50% of the initial size.

## **EXHIBIT C**

### Clinical trial (Phase III)

This clinical study comprised two groups of patients that received:

Group I: Suppositories of 2 g of Preparation H (110 patients). The active ingredient in this case is phenylephrine, a vasoconstrictor.

Group II: Suppositories of 2 g containing excipients, sodium salicylate and 200 000 IU of Recombinant Streptokinase (110 patients).

**Table # 1. Patients' distribution by treatment group according to the Response to the 3rd, 5th day (Principal Variable) and 10th day.**

TREATMENT		Preparation H	SK 200 000 IU	P ( $\chi^2$ )	FB (P(H <sub>0</sub> ))
N		110	110		
3 <sup>rd</sup> day	TR	7 (6.4%)	41 (37.3%)	9.36e-010	52284449 (0.000)
	PR	37 (33.6%)	40 (36.4%)		
	NR	66 (60.0%)	29 (26.4%)		
	Prob TR (Sk-Prep.H) >20% ) / Success		0.988		30.8 (20.7; 41.2)*
5 <sup>th</sup> day	TR	36 (32.7%)	83 (75.5%)	7.35e-010	68018440 (0.000)
	PR	37 (33.6%)	12 (10.9%)		
	NR	37 (33.6%)	15 (13.6%)		
	Prob TR (Sk>70%) / Success Prob TR (Sk-Prep.H) >20% ) / Success		0.903 (P(=70%): 0.949)  0.998		42.7 (30.5; 54.2)*
10 <sup>th</sup> day	TR	64 (58.2%)	92 (83.6%)	0.0001	297.202 (0.003)
	PR	20 (18.2%)	7 (6.4%)		
	NR	26 (23.6%)	11 (10.0%)		
	Prob TR (Sk- Prep.H)>20%)/ Success		0.834		25.5 (13.8; 36.8)*

\*Difference Sk-PH (CI 95% for this Difference)

FB: Bayes Factor in favor of dependency; P (H<sub>0</sub>): Probability of the hypothesis of independence among the variables.

The clinical response was evaluated at 72 hours, on the 5th day and on the 10th day after starting the treatment, according to the following criteria:

- **Total Response**: The complete disappearance of pain and edema (or of a mild intensity), and the reduction in 70% or more of the initial size of the hemorrhoid lesion.
- **PARTIAL response**: The presence of pain and edema but with a reduction in its intensity and a reduction of the size of the lesion of 50 - 69%.
- **No response**: No reduction in the intensity of the pain and/or the edema, and a reduction of the hemorrhoid lesion in less than 50%.

Note: if any criterion was not fulfilled, the patient was evaluated with the following lower category.

**Table # 1** shows the distribution of patients according to the main evaluation variable (Total Response on the 5th day) defined as a reduction of more than 70% of the size of the initial lesion and without the presence of pain and edema [*or of mild intensity*). It also shows the evolution with this variable on the 3<sup>rd</sup> and 10<sup>th</sup> day of the treatment.

It can be observed, in the three times considered, that a significant dependence is found between the success and the treatment received, favoring those treated with SK; the probability of surpassing 20% magnitude is greater than 0.98 on the 3rd and 5th day. On the 10th day we similarly detected the dependence between the variables, although in this case the magnitude of the difference ranged from 13.8 to 36.8 with a confidence of 95%.

The results observed on the 5th day of the treatment (main variable) made it possible to respond to the working hypothesis of the study that stated a superiority of over 20% of SK compared to PH, with a punctual difference estimated in 42.7% (IC 95%: 30.5 – 54.2); and the probability that the group treated with SK would have a success above 70% is greater than 0.90 (which formed part also of the working hypothesis).